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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
LEE *et al*	Art Unit: To be assigned
U.S. Appl. No.: To be assigned	Examiner: To be assigned
Filed: Herewith	Atty. Docket:
For: **Products and Methods for Controlling the Suppression of the Neoplastic Phenotype**	

Declaration Under 37 C.F.R. § 1.132 of Jiing-Kuan Yee, Ph.D.

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned, Jiing-Kuan Yee, declares and says as follows:

1. I am currently Associate Professor of Virology at the Beckman Research Institute of City of Hope National Medical Center in Duarte, California. A copy of my curriculum vitae is attached as Exhibit A to this Declaration.

2. From 1983 to 1987, I was employed as a postdoctoral research fellow in the laboratory of Dr. Theodore Friedmann in the Department of Pediatrics of the Center for Molecular Genetics, School of Medicine, University of California at San Diego ("UCSD"), La Jolla, California. After 1987, I served as an Adjunct Assistant Professor at UCSD.

3. In 1987 and 1988, Dr. Friedmann's research group at the Center for Molecular Genetics, of which I was a member, was widely considered to be one of the

world's foremost groups in terms of expertise and success with retroviral mediated gene transfer techniques and its applications to human gene therapy.

4. In about the late summer or early fall of 1987, our research group was approached by Dr. Wen-Hwa Lee's research group about the possibility of constructing a vector for introducing the retinoblastoma gene into cancer cells. At the time, Dr. Wen-Hwa Lee headed a research group in the Department of Pathology of the Center for Molecular Genetics, School of Medicine, University of California at San Diego, La Jolla, California. Earlier that year, Dr. Lee's group had published a paper describing the cloning, identification and sequence of the human retinoblastoma susceptibility gene ("Rb"). Furthermore, there was at that time an existing collaboration between the Lee laboratory and the Friedmann laboratory to characterize the structure of the Rb gene. Results of those studies were published jointly by the Friedmann and Lee laboratories in 1988. (*See* Exhibit B, attached.) I was friends with several members of Dr. Lee's research group at that time, including Huei-Jen Su Huang, and we frequently discussed in general the various projects on which our respective labs were working. It was clear to me from these discussions that Dr. Lee's group did not have the expertise or experience in designing and preparing gene transfer vectors suitable for transfecting cancer cells with the Rb cDNA. Dr. Lee's group approached our group for assistance in designing and constructing an efficient and effective vector for Rb, and it was apparent to me that they did so because of the well-known expertise of our lab in the area of retroviral mediated gene transfer.

5. Of the members of Dr. Friedmann's research group at that time, I was most proficient at designing vector constructs. Consequently, I was assigned primary

responsibility for conceiving of a design for and constructing the Rb vector. As is customary, I frequently reported to and consulted with Dr. Friedmann about my progress while working on this project and made suitable changes in our strategy as needed based on our discussions. I was the member of Dr. Friedmann's research group who was most involved with our efforts to construct a vector for Rb, and who had the most interaction with members of Dr. Lee's group on this project.

6. At the outset of our group's collaboration with Dr. Lee's group on the Rb vector project, Dr. Friedmann and I consulted on a strategy for designing a vector for Rb, and jointly conceived of a plan to modify our proprietary pLLRNL retroviral vector for this purpose. The pLLRNL vector was a retroviral vector that had been designed and constructed entirely in Dr. Friedmann's lab by members of our research group prior to any collaboration with Dr. Lee's group. At the time of our collaboration with Dr. Lee's group, pLLRNL had not yet been disclosed in any published papers, and therefore it was considered proprietary to our lab. The members of Dr. Lee's laboratory provided absolutely no input regarding the specific design of or construction of a suitable vector for the Rb gene, nor was such input sought by our group.

7. In conceiving of a design for and constructing the Rb vector, my primary concern was to construct a vector capable of stable and efficient transgene expression. There are a number of factors that influence proviral stability in any given case, all of which must be taken into consideration in designing the vector. These include: vector design, the nature of the reporter and selectable marker genes, the existence of internal transcription units, the nature of the internal promoter, the presence or absence of selective pressure, and the nature

of the target cell. At the time of the Rb vector project, in the late Summer-Fall of 1987, there were no universally accepted rules available to us or any other research group for the design of stable and efficiently expressing vectors. Because we were studying these factors far more actively than other laboratories, we had a greater understanding of the importance of these factors than other investigators. We realized that each specific vector needs to be custom designed and tailored to the specific gene and target cell, and our laboratory had the requisite technical expertise to custom design and construct such vectors. We published our analysis of the factors influencing vector design in 1989, after the establishment of the collaboration with Dr. Lee for the Rb vector preparation. (*See* Exhibit C, attached.)

8. Our efforts resulted in the conception of and construction of a novel vector, pLRbRNL, which contained the Rb gene. Excerpts from my lab notebook showing in detail how I constructed the pLRbRNL vector are attached as Exhibit D to this Declaration. I entered the constructs and data depicted in Exhibit D into my lab notebook at the time that I worked on the project, i.e. late Summer-Fall of 1987. Based on my previous experiences with the proprietary pLRRNL vector, I concluded that placing the transgene under the control of the 5' LTR and the use of the RSV promoter as an internal promoter to drive the Neo gene expression seemed to be an optimal design. Although other arrangements of the vector components were possible, we selected our final version based on ongoing studies in our laboratory of how retroviral vector design influences transgene stability and expression. Specifically, we knew from these studies that some of the arrangements resulted in unstable constructs or insufficient levels of expression, and that not only the nature of the gene but

the precise arrangement of the vector components can greatly effect long term stability and expression.

9. After our group conceived of and constructed the pLRbRNL vector, we gave it to Dr. Lee's group to test in cancer cells. Using the same pLRbRNL vector that our group had conceived of and constructed for them, Dr. Lee's group successfully introduced the cloned Rb gene into retinoblastoma and osteosarcoma cells that had inactivated endogenous Rb genes and showed that expression of the exogenous Rb gene affected cell morphology, growth rate, soft agar colony formation, and tumorigenicity. This is believed to be the first ever demonstration of suppression of the neoplastic phenotype by a single gene, and the findings were the subject of a paper published in the journal *Science* on December 16, 1988, on which I am listed as an author along with Dr. Friedmann and members of Dr. Lee's group. A copy of that paper is attached as Exhibit E to this Declaration.

10. The contents of that paper, including the details concerning our conception of the design for and construction of the pLRbRNL vector, were subsequently incorporated substantially *verbatim* into a U.S. patent application filed on behalf of The Regents of the University of California and naming as inventors Dr. Wen-Hwa Lee and certain other members of his group. Neither Dr. Friedmann nor I were consulted regarding the preparation or filing of the patent application, nor were we listed as inventors. In fact, we were never told by Dr. Lee of the filing of this application, and only became aware of it much later in conversations with representatives of the University of California.

11. It was not until 2000, when Dr. Friedmann and I decided that it was necessary to retain our own counsel, that we were able to conclude, with our counsel's aid, that an error in inventorship had occurred due to the fact that we were not named as coinventors on the originally filed application.

12. The undersigned further declares that all statements made herein of his knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements or the like so made are punishable by fine, imprisonment, or both under § 1001 of Title 18, United States Code, and that such willful false statements may jeopardize the validity of any application or patent issued thereon.

11- 29-2001
Date

Jiing-Kuan Yee, Ph.D

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